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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,212	07/13/2001	Venkatraman Ramakrishnan	256602000600	3863
29933	7590	06/07/2005		EXAMINER
PALMER & DODGE, LLP				LY, CHEYNE D
KATHLEEN M. WILLIAMS				
111 HUNTINGTON AVENUE			ART UNIT	PAPER NUMBER
BOSTON, MA 02199			1631	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action Before the Filing of an Appeal Brief</b>	Application No.	Applicant(s)
	09/905,212	RAMAKRISHNAN ET AL.
	Examiner	Art Unit
	Cheyne D. Ly	1631

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

THE REPLY FILED 20 May 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1.  The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a)  The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b)  The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2.  The Notice of Appeal was filed on May 20, 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3.  The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because

(a)  They raise new issues that would require further consideration and/or search (see NOTE below);  
(b)  They raise the issue of new matter (see NOTE below);  
(c)  They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d)  They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4.  The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5.  Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6.  Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7.  For purposes of appeal, the proposed amendment(s): a)  will not be entered, or b)  will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 1-4, 7, 12 and 13.  
Claim(s) withdrawn from consideration: 5, 6 and 8-11.

AFFIDAVIT OR OTHER EVIDENCE

8.  The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9.  The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10.  The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11.  The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.

12.  Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). \_\_\_\_\_.  
13.  Other: See Continuation Sheet.

the number and complexity (20 associated proteins and 16S RNA) of the protein to be crystallized would reasonably increase the unpredictability factor, which would result in even higher failure rate for the 30S subunit proteins that are being crystallized. Therefore, one of skill in the art would not know how to predictably practice the claimed invention on any other 30S subunit without undue experimentation.

Continuation of 13. Other: Claims 5,6 and 8-11 have been withdrawn in the Office Action, mailed May 27, 2003. However, Applicant has indicated said claims as being "(Previously Presented)" which is improper. 37 CFR 1.121 requires that the status of every claim must be indicated. Therefore, Applicant is required to indicate claims 5,6 and 8-11 with the "(Withdrawn)" status. Further, claims 14-22 have the status identifier of "(Canceled)" wherein the claim text is present in the cancelled claims which is improper. 37 CFR 1.121 requires that claim text shall not be presented in cancelled claims.

CR  
6/02/05

*Ardin H. Marschel 6/2/05*  
ARDIN H. MARSCHEL  
PRIMARY EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because:

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. NEW MATTER REJECTION.

This rejection is maintained with respect to claim 12, as recited in the previous office action mailed November 17, 2004.

Applicant argues that "one of skill would consider that determining the resolution of a *T. thermophilus* crystal at 3.0 as 'about 3 Å,' in light of the disclosure. Applicant points to the Abstract for written description basis support. Applicant's argument is not persuasive because the pointed to specification is directed to the crystal obtained from a *Thermus thermophilus* 30S subunit, bound to an antibiotic from a list of antibiotics, having a specified space group. While, the claim is directed to a generic prokaryotic 30S ribosomal subunit, bound to an antibiotic from a list of antibiotics, without specifying any space groups. Therefore, the pointed disclosure does not provide written basis for the limitation of "a resolution of about 3 Å" directed to a generic prokaryotic 30S ribosomal subunit.

Specific to the pointed support (page 12, lines 10-25), the support is not persuasive because the support is directed to "degree of experimental variability" for obtaining the crystal of the invention. However, the pointed to disclosure does not provide written basis for the limitation of "a resolution of about 3 Å."

Claims 1-4, 7, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal structure of the *Thermus thermophilus* 30S subunit, does not reasonably provide enablement for any 30S subunit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained with respect to claims 1-4, 7, 12, and 13, as recited in the previous office action mailed November 17, 2004.

It is noted that Applicant's pointed to support of page 11 in the previous response, filed August 26, 2004, has been considered and fully responded to in the previous Office Action, mailed November 17, 2004. Specific to the cited disclosure on page 11, Applicant argues that the "instant specification discloses how to make and use a crystal of a 30S ribosomal subunit from any prokaryotic species as encompassed by the instant claims." It is noted that the cited disclosure provides a description of means for providing crystals of *T. thermophilus* as exemplified by Examples 1-4 (pages 22-34) that are specific for *T. thermophilus*. However, Applicant does not disclose by guidance or working example for making crystals for different species based on the property of structural conservation of ribosomes. Therefore, one of skill in the art would not know how to predictably practice the claimed invention based on structural conservation of ribosomes without undue experimentation.

Further, structure conservation is only one of many characteristics of organisms such as prokaryotes, which have been used for the classification of said organisms. It is well known in the art that other characteristics (not a comprehensive example) such as gram stain, growth conditions, and metabolic properties have been widely used for classifying organisms of different species. Further, the knowledge of the structure of a protein is one of the many factors that contribute to the protein being able to be crystallized. Factors such as growth conditions and metabolic properties of an organism strongly determine the effort required to predictably crystallize a specific protein from said organism. It is these factors that determine the protein environment from which a protein is to be crystallized. The difference in the protein-surrounding environment due to the proteins being from organisms of different species greatly determines whether said proteins could be predictably crystallized using the same method.

Applicant argues that the structural conservation is in the regions of structure essential for function. It is noted that the area of the structural conservation of proteins is not the only area of said proteins that determines whether said protein could be predictably crystallized. Even with the regions of structure essential for function being conserved, the difference in the protein sequences, due to said sequences from different species, outside of the conserved regions greatly determines whether said proteins could be predictably crystallized using the same method. Therefore, it is the characteristics of structural conservation and the above discussed factors that contribute to unpredictability of the art of protein crystallization as re-iterated below. Therefore, the citation of the high degree of conservation of ribosome structure between prokaryotes of different species alone does enable one of skill in the art to predictably practice the claimed invention without undue experimentation.

Applicant cites *In re Cortright*, 165, F.3d 1353, 1356-57, 49 USPQ2d 1464 (Fed. Cir. 1999) to support that a disclosure is presumed to be enabling absent some clear indication to the contrary. Applicant's citation of *In re Cortright* has been noted. The evidence which indicates that the art of protein crystallization is unpredictable has been provided via Drenth J. and New Focus, Science, 2002 in the previous Office Actions.

Applicant argues that the Office provides no objective basis for making the leap from applying the degree of unpredictability inherent in crystallizing any number of individual proteins to the crystallizing of 30S ribosomal subunits which Applicant asserts to have a highly ordered structure that is conserved among prokaryotic species. Applicant's argument directed to the conserved structures has been addressed above. Specific to the crystallization of the 30S subunit, it is reasonable to expect, via Drenth J. and New Focus, Science, 2002, that it would be unpredictable at best to reproduce crystals of individual proteins due to the high failure rate for proteins that are being crystallized. Applicant discloses that the 30S subunit